CHEMICAL APPLICATIONS OF NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

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Introduction

Nuclear magnetic resonance (NMR) signals from bulk matter (as opposed to results from molecular beam experiments) were first observed in 1945. The results of these pioneering experiments by two groups, working independently and using somewhat different methods, were published in 1946 (1, 2). The two men under whose direction the work was done—Bloch, of Stanford, and Purcell, of Harvard—shared the Nobel Prize in Physics in 1952.

Early NMR studies were made by physicists, primarily for the purpose of determining nuclear properties. About 1950, papers appeared describing shifts of the resonance signals. These shifts were attributed to chemical causes; that is, they were believed to be due to the influence of the electrons surrounding the nuclei under investigation (3–5). Discovery of these shifts was somewhat perturbing to physicists because it meant the loss of several significant figures in some nuclear moment data. On the other hand, the shifts were soon recognized as potentially of great value to chemists.

Since 1950, great improvements have been made in NMR instrumentation and methods, and advances have been made in understanding the chemical significance of NMR phenomena. As a result of these developments, NMR is now widely used by chemists for analysis, structure determination, and other purposes. The present rapid pace of development is likely to continue for several years.

Principles

There are about 100 kinds of nuclei that possess an intrinsic angular momentum or spin (6). In principle, NMR experiments can be performed with any of these nuclei, but protons are undoubtedly of greatest interest. Some nuclei, such as C^{12} and O^{16}, do not have spins and, hence, cannot be detected by NMR. The nuclei C^{13} and O^{17} can be studied, but they are present at very low concentrations in natural abundance. Other nuclei, such as F^{19} and P^{31}, are well suited to NMR

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studies, but compounds containing these elements are of less interest than those containing hydrogen.

The Resonance Condition. In a magnetic field, protons align themselves so that their magnetic moments are either "parallel" or "antiparallel" to the field. They precess about the direction of the field with a frequency that is proportional to the strength of the field.

Because the parallel case represents lower total energy for the system, this orientation is preferred. However, the energy difference between antiparallel and parallel cases is quite small, and the number of excess nuclei with parallel orientation is also small. For protons at $25°C$. and in a field of $10,000$ gauss, the number of excess nuclei in the parallel condition is about 10^{-5} of the total number present.

If a sample containing protons is subjected simultaneously to the influence of a static magnetic field and a radio-frequency field, the amount of radio-frequency energy absorbed is small except when the frequency is equal to the natural precession frequency. When these two frequencies are equal, absorption of radio-frequency energy occurs, and the nuclei are said to be in "resonance." In practice, the radio frequency is held constant and the magnetic field is varied to find the resonance condition. Absorption of radio-frequency energy by protons at resonance is due to a net reorientation of protons from parallel to antiparallel. This process results in a more nearly equal distribution of protons between the two possible orientations.

In a typical instrument for producing resonance, an electromagnet is used to maintain a static field of about 9400 gauss. The corresponding radio frequency for protons is 40 mc.

Chemical Shifts and Spin-Spin Interactions.—At a given radio frequency, the magnetic field (at the nuclei) required to produce resonance of protons is independent of their state of chemical combination. However, the magnetic-field strength in the vicinity of a nucleus depends not only on the applied field but also on effects within the molecule of which the nucleus is a part and on effects external to the molecule.

In sufficiently mobile fluids, all atoms within a molecule are exposed to about the same average external effects because of the rapid motion of the molecules. It is the intramolecular effects that are responsible for the multiplicity of peaks observed in the high-resolution NMR spectra of many organic compounds. In a sense, each proton is a probe, or sensing element, which, with proper coaxing, can be made to reveal the magnitude of the magnetic field in its vicinity.

The two most important intramolecular effects are called "chemical shifts" and "spin-spin interactions." Chemical shifts between nuclei of a given kind are primarily attributed to differences in electronic densities; for example, at a given frequency, resonance of the methylene protons in ethyl ether requires a less intense magnetic field than that required for the methyl protons. The oxygen atom withdraws electrons more effectively from the methylene protons. Chemical shifts for protons are somewhat characteristic of the functional groups in which they are found. Tabulations of values for various groups in a variety of compounds are available. Chemical shifts are proportional to the magnetic-field strength. Hence, more intense fields result in better resolution.

Spin-spin splittings result from indirect interaction of nuclei by way of the bonding electrons (6, 7). They are independent of magnetic-field strength, and can be distinguished from splittings due to chemical shifts on the basis of this characteristic.

Spin-spin interactions between equivalent nuclei (same chemical shift) do not contribute to the NMR spectrum. For protons (or other nuclei with spins of ½), the number of component peaks in the resonance multiplet due to a given proton or an equivalent group of protons is equal to the number of protons in the group causing splitting plus one. Interaction of two groups of nuclei is quantitatively mutual; that is, the separation between adjacent peaks of the two multiplets is equal. The simple rules in the last two sentences do not apply when the spin-spin splitting is approximately equal to, or greater than, the chemical shift separation of the interacting groups. Satisfactory consideration of the more complicated cases requires proper application of quantum mechanics (8, 9).

The areas under peaks in NMR spectra are proportional to the respective number of nuclei whose resonance produces them. This fact makes possible estimation of the relative number of protons contributing to each chemical shift peak in a spectrum. It is also the basis of quantitative analysis by NMR without standardization.

Applications

Structure Determination.—Structure determination in the sense of distinguishing among isomeric possibilities is frequently easily done by means of NMR; for example, Fig. 1 shows the spectrum of a compound resulting from the addition of methyl mercaptan to vinyl acetate. The question was: Which way did the mercaptan add across the double bond?
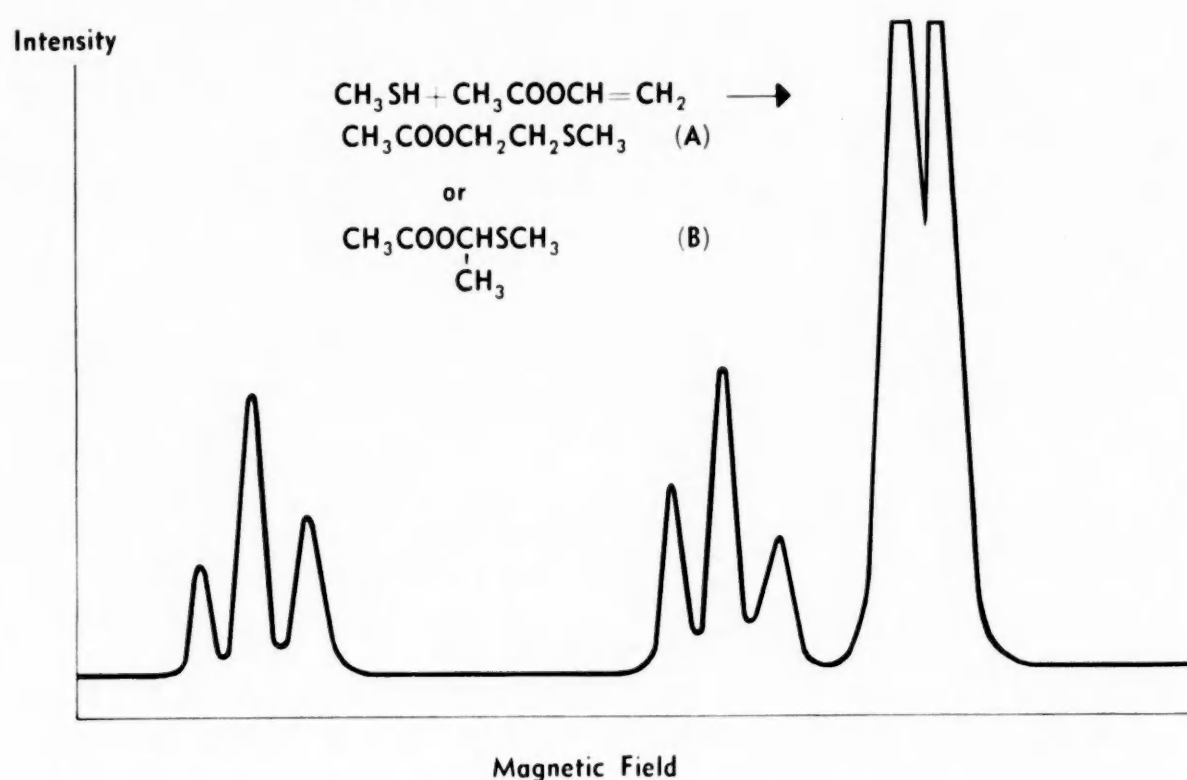

Fig. 1. NMR spectrum of 2-(methylthio)ethyl acetate.

The two terminal CH_3 groups in both possible compounds (A and B) would be expected to give intense single peaks at relatively high fields. The two overlapping peaks on the right are undoubtedly due to these CH_3 groups. The rest of the spectrum should be two triplets of equal intensity for A or a doublet and a quartet with relative intensities of 1:3 for B. The two triplets actually observed prove that the structure is A.

A somewhat more complicated case is that of diketene. Several possible structures have been proposed. X-ray diffraction studies established that the solid has the structure indicated by I. Infrared spectra of liquid and gaseous diketene suggested
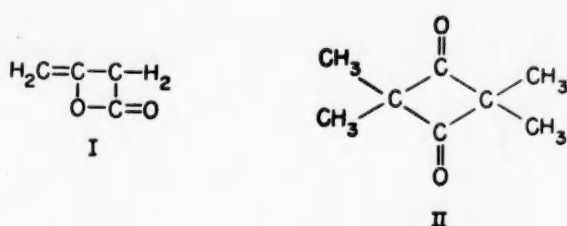
that they were composed of an equilibrium mixture of two or more isomers. The NMR spectrum of liquid diketene (10), however, showed unequivocally that it too has Structure I.

The spectrum of the dimer of dimethylketene showed it to have a very different structure from that of diketene. Dimethylketene dimer produces a single sharp NMR peak, and hence, its structure is believed to be that shown by II.

Determination of the structure of Feist's acid is another example of the way in which NMR often settles questions of structure easily and unambiguously (11).

Interpretation of NMR spectra of complex molecules can be quite difficult. However, reference spectra for a class of compounds of known structure often lead to generalizations that aid in deciding structures of unknown compounds. For example, many steroids have been studied, and structure–spectra correlations have been observed (12). The advantages of intense magnetic fields for studying complex molecules have been clearly demonstrated (13).

Correlation of NMR Results with Other Data.—There are indications that, in some cases, relative electron densities estimated by means of NMR can be correlated with chemical reactivity. Work done on the isomeric xylenes and toluic acids illustrates this application.

Quantitative results on the relative ease of oxidation of these compounds is scarce, but, qualitatively, the following facts are known: All three xylenes are easily oxidized to the corresponding toluic acids. Oxidation of the toluic acids to the corresponding phthalic acids is much more difficult. Of the toluic acids, the *ortho*-isomer is the most difficult to oxidize. Since oxidation involves conversion of a methyl group to a carboxy group in each case, it is reasonable to assume that the electron density about the methyl group being attacked is an important factor. The NMR results are qualitatively in accord with the chemical facts; that is, the chemical shift for the methyl protons is lowest for *o*-toluic acid, intermediate for the other toluic acids, and highest for the xylenes (14).

Quantitative correlation of F^{19} resonance in substituted fluorobenzenes with Hammett sigma constants for the substituents is another example (15).

Quantitative Analysis. At present, NMR is not primarily an analytical tool. There are some analyses, however, for which it is well suited Determination of the keto-enol ratios in tautomeric mixtures is an example. The equilibrium is not disturbed, and calibration is unnecessary. Quantitative analysis involves only correct assignment of peaks due to each tautomer and a simple calculation based on the areas due to one peak from each tautomer. The respective peak areas are proportional to the number of protons responsible for them. Keto-enol ratios for 2,4-pentanedione and 3-methyl-2,4-pentanedione have been determined by means of NMR (16).

In some cases, the thermal isomerizations and other reactions can be followed conveniently by means of NMR (17, 18).

Conclusion

This brief discussion is not comprehensive in either scope or depth. The book or one of the reviews on the subject should be consulted for further details (6, 19-22).

It would be unwise to go on record with specific predictions concerning the future of NMR, but it is certainly safe to predict that it will make possible major contributions to chemical knowledge. One should not leave the impression, however, that NMR methods will supplant infrared, x-ray diffraction, or any of the other older methods. NMR gives an essentially different kind of information, and hence, it is best used in conjunction with, not instead of, other methods. Because NMR spectra are so intimately related to electronic configurations and interactions, it seems likely that the most important basic information obtainable by this method has to do with the fundamental nature of electronic systems in molecules. The understanding of such systems and their interactions is the essence of chemical knowledge.

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